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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/054,444	01/22/2002	Paul M. Guyre	DC-0172	9998

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EXAMINER
HUYNH, PHUONG N

ART UNIT	PAPER NUMBER
1644	9

DATE MAILED: 09/23/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/054,444	GUYRE ET AL.	
	Examiner	Art Unit	
	Phuong Huynh	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the corresp ndence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 July 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 3* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 3* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 7/10/03 has been entered.

2. Claims 1 and 3 are pending and are being acted upon in this Office Action.

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1 and 3 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for a compound comprising a baculovirus expressed recombinant Fel dI wherein the baculovirus expressed recombinant Fel dI comprises a sFv humanized anti-CD64 monoclonal antibody H22 fused to Fel dI chain 1 and Fel dI chain 2 wherein chain 1 and chain 2 are linked in series by a glycine/serine linker encoded by SEQ ID NO: 5 as shown in Figure 1 for diagnosis of cat allergy, **does not** reasonably provide enablement for *any* compound as set forth in claims 1 and 3 for diagnosis and treatment of cat allergy. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The specification discloses only a compound as shown in Figure 1 wherein the compound comprising a baculovirus expressed recombinant Fel dI wherein the baculovirus expressed recombinant Fel dI comprises a sFv humanized anti-CD64 monoclonal antibody H22 fused to Fel dI chain 1 and Fel dI chain 2 wherein chain 1 and chain 2 are linked in series via a flexible peptide linker a glycine/serine linker $(glycine_4\ Ser)_3$ encoded by SEQ ID NO: 5 and further linked to Myc or His tag for diagnosis of cat allergy in humans. The recombinant Fel dI is purified on nickel affinity column. The rFel dI shows that IgG and IgE antibody binding is identical to natural Fel dI using IgG antibody in pooled sera from either Japanese or US cat allergic patients.

The specification does not teach how to make and use *any* compound mentioned above for diagnosing or treating cat allergy because there is insufficient guidance on the hybridization conditions using primers of SEQ ID NO: 1-4 for amplifying the nucleic acid sequences that encoded the Fel dI chain 1 and chain 2 in the claimed compound.

The state of the prior art as exemplified by Wallace *et al* and Sambrook *et al* is such that determining the specificity of hybridization probes is empirical by nature and the effect of mismatches within an oligonucleotide probe is unpredictable. Since the hybridization conditions amplifiable by PCR using the primers for making the claimed compound are not disclosed, it follows that compound is not enabled. It also follows that any compound further comprising a sFv of monoclonal antibody H22 that is humanized anti-CD64 antibody is not enable.

For these reasons, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

5. Claims 1 and 3 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of *any* compound as set forth in claims 1 and 3 for diagnosis and treatment of cat allergy.

The specification discloses only a compound as shown in Figure 1 wherein the compound comprising a baculovirus expressed recombinant Fel dI wherein the baculovirus expressed recombinant Fel dI comprises a sFv humanized anti-CD64 monoclonal antibody H22 fused to Fel dI chain 1 and Fel dI chain 2 wherein chain 1 and chain 2 are linked in series via a flexible peptide linker a glycine/serine linker $(glycine_4\ Ser)_3$ encoded by SEQ ID NO: 5 and further linked to Myc or His tag for diagnosis of cat allergy in humans. The recombinant Fel dI is purified on nickel affinity column. The rFel dI shows that IgG and IgE antibody binding is identical to natural Fel dI using IgG antibody in pooled sera from either Japanese or US cat allergic patients.

The specification does not teach the specific PCR condition using primers 1-4 to amplify any nucleic acid sequences that encoded Fel dI chain 1 and chain 2. Further, claim 1 recites more than one nucleic acid sequences encoding chain 1 or chain 2 which are amplifiable by the specific set of primers. However, the specific nucleic acid sequences encoding chain 1 and chain 2 are not adequately described, in addition to the PCR condition. Given the indefinite number of undisclosed nucleic acid sequences and PCR condition for making the claimed compound, the compound as set forth in claim 1 is not adequately described. Since the compound in claim 1 is not adequately described, it follows that the undisclosed compound further comprising a sFv of monoclonal antibody H22 that is a humanized anti-CD64 antibody is not adequately described.

Given the lack of a written description of *any* additional representative species of nucleic acid sequences that encoded Fel dI chain 1 and chain 2 in the claimed compound, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.*

Applicant is directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Applicants' arguments filed 7/10/03 have been fully considered but are not found persuasive.

Applicants' position is that (1) oligonucleotides are highly sequence specific at an optimal annealing temperature and provide a defining structure for the intervening nucleic acid sequences of Fel dI chain 1 and chain. (2) Using the combination of 5' and 3' sequences flanking chain 1 or chain 2, it would be well within the means of the skilled in the art to obtain the desired chain 1 and chain 2 nucleic acid sequences. (3) Claim 1 has been amended to indicate that the glycine/serine linker is encoded by the nucleic acid sequence of SEQ ID NO: 5.

However, the specific optimal annealing temperature used by Applicants is not in the claim. Further, claim 1 recites more than one nucleic acid sequences encoding chain 1 or chain 2 which are amplifiable by the specific set of primers. However, the specific nucleic acid sequences encoding chain 1 and chain 2 are not disclosed. Given the indefinite number of undisclosed nucleic acid sequences and PCR condition for making the claimed compound, the compound as set forth in claim 1 is not adequately described. Since the compound in claim 1 is not adequately described, it follows that the undisclosed compound further comprising a sFv of monoclonal antibody H22 that is a humanized anti-CD64 antibody is not adequately described.

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

7. Claims 1 and 3 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The recitation of "nucleic acid sequences that are amplifiable by PCR" in claim 1 is indefinite and ambiguous. One of ordinary skill in the art cannot appraise the metes and bounds of the claimed invention because the specific nucleotide or nucleotides that encode either Fel dI chain 1 or chain 2 obtained at which optimal annealing temperature (PCR condition) is/are not disclosed.

8. Claim 1 is rejected under 35 U.S.C. 103(a) as being unpatentable over US 5,547,669 (of record, Aug 1996, PTO 892) in view of US Pat No 5,395,750 (of record, Mar 1995; PTO 892).

The '669 patent teaches various compounds such as TRFP also known as Fel dI chain 1 encoded by the reference nucleic acid of SEQ ID NO: 3, Fel dI chain 2 encoded by the reference nucleic acid sequence of SEQ ID NO: 5 which are amplified by the claimed primers of SEQ ID NO: 1-4 and fusion protein such as recombinant cat allergen Fel dI fusion protein comprising chains 1 and 2 linked together via a linker such as any non-epitope amino acid sequence or other appropriate linking or joining agent (See column 10, lines 13-66, in particular). The reference compound binds to patient IgE at a level comparable to that of natural Fel dI at 1:00 dilution (See figure 14, column 23, lines 61-62, in particular). The '669 patent teaches the recombinant Fel dI is useful for treating and diagnosing sensitivity in an individual to cat allergen such as Fel dI (See column 12, lines 31-33, in particular).

The claimed invention as recited in claim 1 differs from the teachings of the reference only that compound comprising a vaculovirus expressed recombinant Fel dI, wherein the baculovirus expressed recombinant Fel dI comprises chain 1, and chain 2, expressed in series and linked together by a glycine/serine linker encoded by SEQ ID NO: 5, wherein said recombinant Fel dI binds to human IgE and IgG at a level comparable to that of natural Fel dI.

The '750 patent teaches a method of making a compound such as synthetic single chain antibody sequence such as heavy and light region sequences of any antibody is linked by a glycine (G) /serine (S) linker sequence such as GGGGSGGGGSGGGGS that is identical to the amino acid sequence encoded by the claimed sequence of SEQ ID NO: 5 (See reference SEQ ID NO: 13, column 8, lines 65-68, in particular) wherein the reference compound is expressed in E coli, in S cerevisiae and phage display library (See column 9, lines 1-4, lines 50-55, in particular). The '750 patent teaches the reference linker sequence is flexible (See column 8, lines 65-66, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the linker as taught by the '669 patent for the flexible linker glycine and serine $(glycine_4\,Ser)_3$ as taught by the '750 patent. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because the '669 patent teaches the recombinant Fel dI is useful for treating and diagnosing sensitivity in an

individual to cat allergen such as Fel dI (See column 12, lines 31-33, in particular). The '750 patent teaches the linker sequence such as GGGGSGGGGSGGGGS is flexible (See column 9, lines 1-4, lines 50-55, in particular). The recitation of a compound being expressed by baculovirus has no patentable weight because a compound is a compound, irrespective of how it is made. The recitation of chain 1 encoded by nucleic acid sequences that are amplified by PCR using primers of SEQ ID NO: 1 and SEQ ID NO: 2 fails to identify the specific nucleic acid sequence or sequences that encodes the claimed Fel dI chain 1 under the specific PCR condition used by Applicant. Likewise, the recitation of chain 2 encoded by nucleic acid sequences that are amplified by PCR using primers of SEQ ID NO: 3 and SEQ ID NO: 4 fails to identify the specific nucleic acid sequence or sequences that encodes the claimed Fel dI chain 1 under the specific PCR condition. Since the structure of the claimed compound appears to be the same as that of the reference compound, the reference compound would obviously bind to human IgE and IgG at a level comparable to that of natural Fel dI as claimed. Since the Patent Office does not have the facilities for examining and comparing the claimed compound of the instant invention to those of the prior art, the burden is on applicant to show that the prior art compound is different from the claimed compound. See In re Best, 562 F.2d 1252, 195 USPQ 430(CCPA 1977).

Applicants' arguments filed 7/10/03 have been fully considered but are not found persuasive.

Applicants' position is that (1) the novelty and unexpected feature of this invention is that baculovirus-produced, recombinant Fel dI protein has dramatically improved immunoreactivity for IgG and IgE antibody. (2) Amended claim 1 recites that the recombinant Fel dI protein of the inventions binds to human and IgE and IgG at a level comparable to that of natural Fel dI. (3) the '669 patent does not teach that a recombinant Fel dI protein containing chains 1 and chain 2 joined by a linker binds human IgE and IgG antibody at a level comparable to that of natural Fel dI. In fact, the experimental results provided in Figure 14 and column 23, lines 58-66 of the '669 patent indicate that the recombinant Fel dI proteins bound significantly less human IgE antibody than natural Fel dI protein. Further, this reference teaches away from the claimed invention as it demonstrates that a linker placed between chains 1 and 2 of Fel dI decrease IgE binding compared to recombinant Fel dI or recombinant Fel dI chain 2 alone. (4) The secondary references '750 and '243 fail to overcome the deficiencies in the teachings of the primary reference as they do not indicate that a baculovirus-produced recombinant Fel dI protein has activity comparable to natural Fel dI protein. (5) While Bei et al teach that the specificity and

binding of the baculovirus produced antibodies were comparable to those derived from mammalian cells, in light of the decreased binding of recombinant Fel dI proteins taught by the '669 patent, one of skill in the art would not motivated to combine the teachings of Bei et al with the '669 patent to arrive at the claimed invention.

Although claim 1 has been amended, the nucleic acid sequences that are amplified by PCR using primers of SEQ ID NO: 1 and SEQ ID NO: 2 in claim 1 fails to identify the specific nucleic acid sequence or sequences that encodes the claimed Fel dI chain 1 under the specific PCR condition used by Applicant. Likewise, the recitation of chain 2 encoded by nucleic acid sequences that are amplified by PCR using primers of SEQ ID NO: 3 and SEQ ID NO: 4 fails to identify the specific nucleic acid sequence or sequences that encodes the claimed Fel dI chain 1 under the specific PCR condition. Since the structure of the claimed compound appears to be the same as that of the reference compound, the reference compound would obviously bind to human IgE and IgG at a level comparable to that of natural Fel dI as claimed. Since the Patent Office does not have the facilities for examining and comparing the claimed compound of the instant invention to those of the prior art, the burden is on applicant to show that the prior art compound is different from the claimed compound. See In re Best, 562 F.2d 1252, 195 USPQ 430(CCPA 1977). Further, the '669 patent teaches that the reference compound binds to patient IgE at a level comparable to that of natural Fel dI at 1:00 dilution (See figure 14, column 23, lines 61-62, in particular). Note the specific level is not recited in the claim. As to the specific linker, the '750 patent teaches the claimed flexible linker encoded by the claimed SEQ ID NO: 5 (See reference SEQ ID NO: 13, column 8, lines 65-68, in particular).

9. Claim 3 is rejected under 35 U.S.C. 103(a) as being unpatentable over US 5,547,669 (of record, Aug 1996, PTO 892) in view of in view of US Pat No 5,395,750 (of record, Mar 1995; PTO 892) as applied to claim 1 above and further in view of US Pat No. 5,837,243 (of record, Nov 1998; PTO 892).

The combined teachings of the '669 patent and the '750 patent have been discussed supra.

The claimed invention as recited in claim 3 differs from the combined teachings of the references only that the compound further comprising a sFv of monoclonal antibody H22 which is a humanized anti-CD64 antibody.

The '243 patent teaches bispecific molecules such as cat allergen linked to humanized or single chain (sFv) antibody H22 that binds to Fc receptor such as FcγRI (which also known as CD64) (See column 7, lines 52-67 bridging column 8, lines 1-19, claim 3 of '243, column 6, lines 64-67, in particular). The '243 patent further teaches a method of making bispecific molecules using various expression constructs such as pSVgpt and pSVhyg encoding single chain antibody (sFv) H22 that is specific for humanized Fc receptor such as FcγRI (See column 18, lines 24-33, in particular). The '243 patent teaches the fusion molecules is linked together via a linker such as glycine and serine $(glycine_4\ Ser)_3$ (See Fig 40A, in particular). The '243 patent teaches the antibody H22 is useful for targeting any antigen to the antigen presenting cell by binding to a surface receptor such as FcγRI on the antigen presenting cells, in turn, the antigen presenting cells can internalize antigen for processing and presentation to induce tolerance to said antigen (See column 7, lines 57-67 bridging column 8, lines 1-2, column 8, lines 57-62, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to link the single chain humanized antibody H22 that is specific for Fc receptor such as FcγRI (CD64) to chain 1 and chain 2 of Fel dI (cat allergen) in series as taught by the '669 using a flexible glycine and serine linker $(glycine_4\ Ser)_3$ encoded by SEQ ID NO: 5 as taught by the '750 patent for a compound comprising a recombinant Fel dI comprises chain 1 and chain 2 expressed in series and linked together by a glycine/serine linker and further comprising a sFv of monoclonal antibody H22 which is a humanized anti-CD64 antibody. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because the '243 patent teaches the antibody H22 is useful for targeting any antigen to the antigen presenting cell by binding to a surface receptor such as FcγRI on the antigen presenting cells, in turn, the antigen presenting cells can internalize antigen for processing and presentation to induce tolerance to any antigen such as allergen (See column 7, lines 57-67 bridging column 8, lines 1-2, column 8, lines 57-62, in particular).

Applicants' arguments filed 7/10/03 have been fully considered but are not found persuasive.

Applicants' position is that (1) the novelty and unexpected feature of this invention is that baculovirus-produced, recombinant Fel dI protein has dramatically improved immunoreactivity for IgG and IgE antibody. (2) Amended claim 1 recites that the recombinant Fel dI protein of the

inventions binds to human and IgE and IgG at a level comparable to that of natural Fel dI. (3) the '669 patent does not teach that a recombinant Fel dI protein containing chains 1 and chain 2 joined by a linker binds human IgE and IgG antibody at a level comparable to that of natural Fel dI. In fact, the experimental results provided in Figure 14 and column 23, lines 58-66 of the '669 patent indicate that the recombinant Fel dI proteins bound significantly less human IgE antibody than natural Fel dI protein. Further, this reference teaches away from the claimed invention as it demonstrates that a linker placed between chains 1 and 2 of Fel dI decrease IgE binding compared to recombinant Fel dI or recombinant Fel dI chain 2 alone. (4) The secondary references '750 and '243 fail to overcome the deficiencies in the teachings of the primary reference as they do not indicate that a baculovirus-produced recombinant Fel dI protein has activity comparable to natural Fel dI protein. (5) While Bei et al teach that the specificity and binding of the baculovirus produced antibodies were comparable to those derived from mammalian cells, in light of the decreased binding of recombinant Fel dI proteins taught by the '669 patent, one of skill in the art would not motivated to combine the teachings of Bei et al with the '669 patent to arrive at the claimed invention.

Although claim 1 has been amended, the nucleic acid sequences that are amplified by PCR using primers of SEQ ID NO: 1 and SEQ ID NO: 2 in claim 1 fails to identify the specific nucleic acid sequence or sequences that encode(s) the claimed Fel dI chain 1 under the specific PCR condition used by Applicant. Likewise, the recitation of chain 2 encoded by nucleic acid sequences that are amplified by PCR using primers of SEQ ID NO: 3 and SEQ ID NO: 4 fails to identify the specific nucleic acid sequence or sequences that encodes the claimed Fel dI chain 1 under the specific PCR condition. Since the structure of the claimed compound appears to be the same as that of the reference compound, the reference compound would obviously bind to human IgE and IgG at a level comparable to that of natural Fel dI as claimed. Since the Patent Office does not have the facilities for examining and comparing the claimed compound of the instant invention to those of the prior art, the burden is on applicant to show that the prior art compound is different from the claimed compound. See In re Best, 562 F.2d 1252, 195 USPQ 430(CCPA 1977). Further, the '669 patent teaches that the reference compound binds to patient IgE at a level comparable to that of natural Fel dI at 1:00 dilution (See figure 14, column 23, lines 61-62, in particular). Note the specific level is not recited in the claim. As to the specific linker, the '750 patent teaches the claimed flexible linker encoded by the claimed SEQ ID NO: 5 (See reference SEQ ID NO: 13, column 8, lines 65-68, in particular).

In response to applicant's argument that '243 patent fail to overcome the deficiencies in the teachings of the primary reference as they do not indicate that a baculovirus-produced recombinant Fel dI protein has activity comparable to natural Fel dI protein, Bei *et al* teach the salient features of the baculovirus expression system for making any protein included high efficiency of expression, ease of purification, time saving and cost-effective method of scaling up production of functional proteins such as folding of protein properly (See page 253, column 2, last paragraph, in particular). The fact that applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985).

10. Claim 1 is rejected under 35 U.S.C. 103(a) as being unpatentable over US 5,547,669 (of record, Aug 1996, PTO 892) in view of US Pat No 5,395,750 (of record, Mar 1995; PTO 892) and Bei *et al* (of record; J Immunological Methods 186: 245-255, Oct 1995; PTO 892).

The teachings of the '669 patent and the '750 patents have been discussed supra. The '669 patent further teaches the recombinant Fel dI is expressed in *E. Coli* (See column 2, lines 15-25, lines 65-67 bridging column 22, lines 1-7, column 12, lines 40-43, column 18, line 23, in particular). The '669 patent teaches the recombinant Fel dI is useful for treating and diagnosing sensitivity in an individual to cat allergen such as Fel dI (See column 12, lines 31-33, in particular).

The claimed invention as recited in claim 1 differs from the teachings of the reference only that the compound is expressed by a baculovirus.

Bei *et al* teach the salient features of the baculovirus expression system for making any protein included high efficiency of expression, ease of purification, time saving and cost-effective method of scaling up production of functional proteins (See page 253, column 2, last paragraph, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the *E. Coli* expression vector as taught by the '669 patent or the S cerevisiae vector or phage display vector as taught by the '750 patent for a compound comprising the recombinant Fel dI comprises chain 1 and chain 2 expressed in series and linked together by a glycine/serine linker of SEQ ID NO: 5 as taught by the '669 patent, the 750 patent and Bei *et al.* From the combined teachings of the references, it is apparent that one of ordinary

skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because Bei *et al* teach the salient features of the baculovirus expression system included high efficiency of expression, ease of purification, time saving and cost-effective method of scaling up production of functional proteins (See page 253, column 2, last paragraph, in particular). The '669 patent teaches the recombinant Fel dI is useful for treating and diagnosing sensitivity in an individual to cat allergen such as Fel dI (See column 12, lines 31-33, in particular).

Applicants' arguments filed 7/10/03 have been fully considered but are not found persuasive.

Applicants' position is that (1) the novelty and unexpected feature of this invention is that baculovirus-produced, recombinant Fel dI protein has dramatically improved immunoreactivity for IgG and IgE antibody. (2) Amended claim 1 recites that the recombinant Fel dI protein of the inventions binds to human and IgE and IgG at a level comparable to that of natural Fel dI. (3) the '669 patent does not teach that a recombinant Fel dI protein containing chains 1 and chain 2 joined by a linker binds human IgE and IgG antibody at a level comparable to that of natural Fel dI. In fact, the experimental results provided in Figure 14 and column 23, lines 58-66 of the '669 patent indicate that the recombinant Fel dI proteins bound significantly less human IgE antibody than natural Fel dI protein. Further, this reference teaches away from the claimed invention as it demonstrates that a linker placed between chains 1 and 2 of Fel dI decrease IgE binding compared to recombinant Fel dI or recombinant Fel dI chain 2 alone. (4) The secondary references '750 and '243 fail to overcome the deficiencies in the teachings of the primary reference as they do not indicate that a baculovirus-produced recombinant Fel dI protein has activity comparable to natural Fel dI protein. (5) While Bei et al teach that the specificity and binding of the baculovirus produced antibodies were comparable to those derived from mammalian cells, in light of the decreased binding of recombinant Fel dI proteins taught by the '669 patent, one of skill in the art would not motivated to combine the teachings of Bei et al with the '669 patent to arrive at the claimed invention.

Although claim 1 has been amended, the nucleic acid sequences that are amplified by PCR using primers of SEQ ID NO: 1 and SEQ ID NO: 2 in claim 1 fails to identify the specific nucleic acid sequence or sequences that encodes the claimed Fel dI chain 1 under the specific PCR condition used by Applicant. Likewise, the recitation of chain 2 encoded by nucleic acid

sequences that are amplified by PCR using primers of SEQ ID NO: 3 and SEQ ID NO: 4 fails to identify the specific nucleic acid sequence or sequences that encodes the claimed Fel dI chain 1 under the specific PCR condition. Since the structure of the claimed compound appears to be the same as that of the reference compound, the reference compound would obviously bind to human IgE and IgG at a level comparable to that of natural Fel dI as claimed. Since the Patent Office does not have the facilities for examining and comparing the claimed compound of the instant invention to those of the prior art, the burden is on applicant to show that the prior art compound is different from the claimed compound. See In re Best, 562 F.2d 1252, 195 USPQ 430(CCPA 1977). Further, the '669 patent teaches that the reference compound binds to patient IgE at a level comparable to that of natural Fel dI at 1:00 dilution (See figure 14, column 23, lines 61-62, in particular). Note the specific level is not recited in the claim. As to the specific linker, the '750 patent teaches the claimed flexible linker encoded by the claimed SEQ ID NO: 5 (See reference SEQ ID NO: 13, column 8, lines 65-68, in particular).

In response to applicant's argument that '243 patent fail to overcome the deficiencies in the teachings of the primary reference as they do not indicate that a baculovirus-produced recombinant Fel dI protein has activity comparable to natural Fel dI protein, Bei *et al* teach the salient features of the baculovirus expression system for making any protein included high efficiency of expression, ease of purification, time saving and cost-effective method of scaling up production of functional proteins such as folding of protein properly (See page 253, column 2, last paragraph, in particular). The fact that applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985).

In response to applicants' argument that there is no suggestion or motivation, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See In re Fine 5 USPQ2d 1596 (Fed. Cir 1988) and In re Jones 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, the teachings of the '243 patent pertaining to linking the cat allergen to single chain antibody sFv H22 that binds to CD64 (See column 7, lines 52-67 bridging column 8, lines 1-19, claim 3 of '243, column 6, lines 64-67, in particular) are useful for targeting allergen to the antigen presenting cell by binding to a surface

receptor such as FcγRI on the antigen presenting cells, in turn, the antigen presenting cells can internalize antigen for processing and presentation to induce tolerance to said antigen (See column 7, lines 57-67 bridging column 8, lines 1-2, column 8, lines 57-62, in particular). The teachings of the '699 patent pertaining to recombinant Fel dI comprising chain 1 and chain 2 encoded by the reference polynucleotides of SEQ ID NO: 3 and 5, respectively, linked together by any linker that is expressed as a recombinant protein are useful for treating and diagnosing sensitivity in an individual to cat allergen such as Fel dI (See column 12, lines 31-33, in particular). The teachings of the '760 pertaining to the linker such as glycine/serine are useful for linking any polypeptide because it is flexible (See reference SEQ ID NO: 13, column 8, lines 65-68, in particular). The teachings of the Bei *et al* pertaining *to* the baculovirus expression system for making any protein included high efficiency of expression, ease of purification, time saving and cost-effective method of scaling up production of functional proteins (See page 253, column 2, last paragraph, in particular). In re Sernaker 17 USPQ 1, 5-6 (Fed. Cir. 1983), the strongest rationale for combining reference is a recognition, expressly or implicitly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent that some advantage or expected beneficial result would have been produced by their combination.

11. No claim is allowed.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to "Neon" Phuong Huynh whose telephone number is (703) 308-4844. The examiner can normally be reached Monday through Friday from 9:00 am to 6:00 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist (customer service) whose telephone number is (703) 872-9305.

13. Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform to the notice published in the Official

Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-7401. The IFW official Fax number is (703) 872-9306. For After Final, the Fax number is (703) 872-9307.

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